EXTENDED REPORT

Effect of non-steroidal anti-inflammatory ophthalmic solution on intraocular pressure reduction by latanoprost in patients with primary open angle glaucoma or ocular hypertension

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Aim: To investigate the effects of a non-steroidal anti-inflammatory drug (NSAID) ophthalmic solution on latanoprost induced intraocular pressure (IOP) reduction in glaucoma patients.
Methods: Examination was conducted on 16 eyes of 16 glaucoma patients who had been given only latanoprost for at least 6 weeks. The NSAID ophthalmic solution, sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, was additionally given for 12 weeks into one eye (NSAID group), while sodium hyaluronic acid ophthalmic solution was administered into the other eye (control group) in a double masked fashion. The IOP measurement was performed before the start of additional administration of ophthalmic solutions, 2, 4, 6, 8, 10, and 12 weeks after the start of additional administration, and 2, 4, and 6 weeks after discontinuing additional administration.
Results: No significant difference was observed in the IOPs before additional administration of ophthalmic solution between the NSAID group and the control group. Following the additional administration of ophthalmic solution, IOP in the NSAID group was consistently higher than that in the control group, and a maximum difference in IOP between the two groups was 1.08 (SD 1.75) mm Hg ($p = 0.03$). This trend was observed even after additional administration was discontinued.
Conclusion: NSAID ophthalmic solution may partly affect IOP reduction by latanoprost.

Latanoprost is a phenyl substituted analogue of prostaglandin F2α ($PGF_{2\alpha}$), and is widely used for the treatment of glaucoma because of its excellent potent intraocular pressure (IOP) reduction.[1–3]

Although the mechanism of IOP reduction by latanoprost is thought to increase the uveoscleral outflow as a result of remodelling the extracellular matrix of ciliary muscle mediated by FP receptors, the details of this mechanism remain unclear.[1 4–6] $PGF_{2\alpha}$ related drugs have been reported to produce endogenous prostaglandins (PGs), and several reports have suggested that induction of endogenous PGs is involved in IOP reduction.[7–9]

Although it appears certain that endogenous PGs are produced by administering $PGF_{2\alpha}$ related drugs based on the results of basic experiments,[7 8] since the action of PG on the eyes shows species differences, the results of basic and animal experiments cannot be directly applied to the human eye.[2] Therefore, we have conducted a study on the action of endogenous PGs on IOP resulting from the administration of $PGF_{2\alpha}$ in healthy volunteers, and found that the IOP reduction of latanoprost is inhibited by the administration of NSAID ophthalmic solution.[10] However, there have yet to be studies on the effect of NSAID ophthalmic solution on the IOP reduction of latanoprost in glaucomatous human eyes.

In this study, a prospective double blind study was conducted to assess the effect of administering NSAID ophthalmic solution on the IOP reduction of latanoprost, targeting patients with primary open angle glaucoma (POAG) or ocular hypertension (OH).

SUBJECTS AND METHODS

All experiments were conducted in accordance with the Helsinki treaty and written informed consent was obtained from all participants.

Subjects and exclusion criteria

Examination was conducted on 16 eyes of 16 patients with POAG or OH, who had been given only 0.005% latanoprost for 6 weeks (eight men, eight women, aged 65.2 (SD 8.8) years (range 38–81 years)); 10 patients had POAG and six had OH. Patients who had a history of intraocular surgery, laser iridotomy, laser trabeculoplasty or uveitis, as well as those who changed their systemic medication during the course of the study were excluded from the study.

Study schedule

The study protocol is shown in figure 1. During the study, IOP measurement and slit lamp examinations were conducted at 2 week intervals, whereas visual acuity and fundus examinations were conducted at 4 week intervals. IOP was measured with a Goldmann applanation tonometer by the same ophthalmologist (TC) using the same instrument and at the same time after masking information of the eye to which ophthalmic solutions were administered.

The NSAID ophthalmic solution, sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate (bromfenac sodium hydrate, Senju Pharmaceutical, Osaka, Japan), was additionally administered to one randomly selected eye (NSAID group), while 0.1% sodium hyaluronic acid ophthalmic solution (Santen Pharmaceutical, Osaka, Japan) was additionally administered to the other eye (control group) of patients given 0.005% latanoprost ophthalmic solution after masking ophthalmic solution information. The 0.005% latanoprost ophthalmic solution was given once before bedtime, whereas bromfenac sodium hydrate ophthalmic

Abbreviations: IOP, intraocular pressure; MD, mean deviation; NSAID, non-steroidal anti-inflammatory drugs; OH, ocular hypertension; PG, prostaglandins; POAG, primary open angle glaucoma

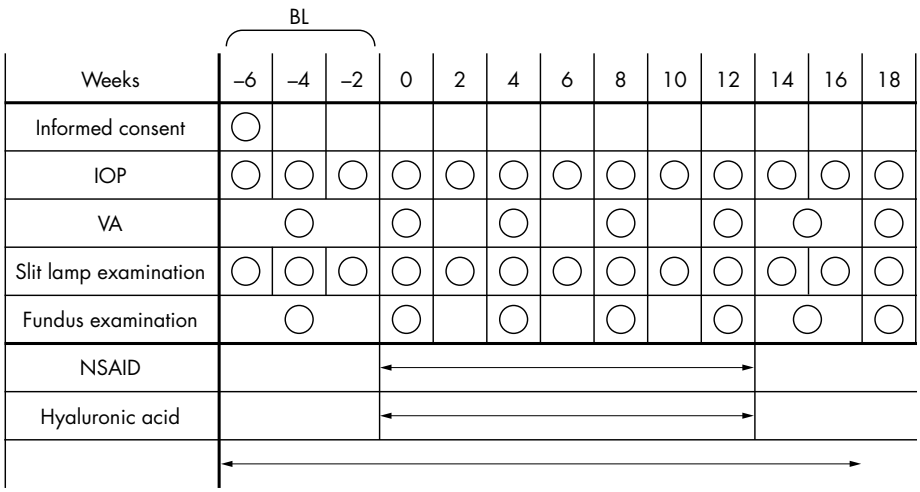

Figure 1 Study protocol. To determine baseline condition, examination was repeated three times. BL, baseline, IOP, intraocular pressure, VA, visual acuity, NSAID, non-steroidal anti-inflammatory drug, hyaluronic acid, sodium hyaluronic acid.

solution or 0.1% sodium hyaluronic acid ophthalmic solution was given twice a day in the morning and evening. There was a minimum interval of 5 minutes between latanoprost administration and the additional administration of ophthalmic solutions. The mean IOP of three measurements before additional administration of ophthalmic solution was defined as the baseline IOP.

Slit lamp microscopic examinations were performed to confirm the absence of local adverse effects. The administration of ophthalmic solution was discontinued when corneal erosion or other adverse effects were noted. IOP was measured 2, 4, 6, 8, 10, and 12 weeks after the start of additional administration, and 2, 4 and 6 weeks after discontinuing additional administration of ophthalmic solutions.

Investigated parameters

The two groups were compared in terms of IOP measured at 2 week intervals during the course of the study, the amount of change in IOP following additional administration of ophthalmic solution based on the baseline IOP, differences in IOP between the NSAID group and the control group, age, sex, refractive error, and mean deviation (MD) values measured with a Humphrey field analyser (Carl Zeiss Medicine, Dublin, CA, USA) program 30-2.

Statistical analysis

Comparisons of the amount of change in IOP in each group were made using the paired *t* test, while sex was tested using the Mann-Whitney U test, both at a level of significance of $p<0.05$. Correlations between baseline IOP and IOP difference during co-administration between NSAID group and control group, correlation of the NSAID induced inhibition of IOP reduction by latanoprost with the IOP reduction rate by latanoprost; IOP before administration of NSAID ophthalmic solution, age, and MD value were analysed using Spearman's correlation coefficient by rank at a level of significance of $p<0.05$. All values were expressed as means (SD).

RESULTS

Patient background (table 1)

During the first 6 weeks to determine the baseline IOP, three patients who were given only 0.005% latanoprost ophthalmic solution were withdrawn from the study for the following reasons: one had corneal erosion, one violated the protocol of the study, and one moved away. Accordingly, a total of 13 eyes of 13 patients were assessed. The patient breakdown is as follows: six men and seven women; average age, 65.2 (8.8) years; and age range 46–81 years. There were nine patients with POAG and four with OH. The mean corrected visual

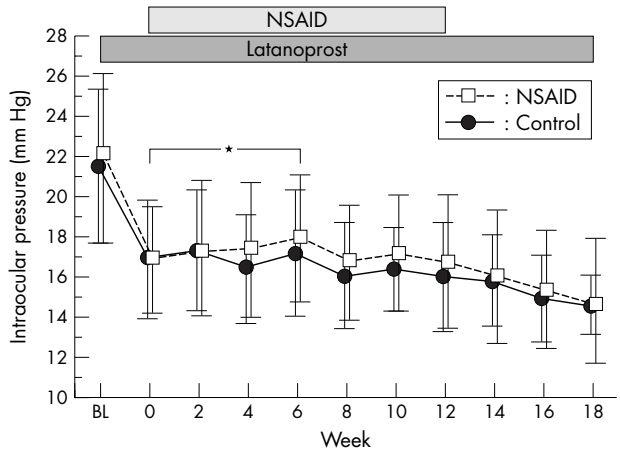

Figure 2 IOP change profile. NSAID, non-steroidal anti-inflammatory drug, BL, baseline, *p, 0.028.

Table 1 Demographics of patients

	Total	NSAID	Control
POAG:OH	9:4		
M:F	6:7		
Age	65.2 (8.8)		
logMAR	−0.04 (0.14)	−0.05 (0.17)	−0.03 (0.10)
Spherical equivalent (D)	−1.17 (3.86)	−1.33 (3.72)	−1.02 (4.15)
MD (dB)	−1.73 (5.00)	−2.38 (6.33)	−1.08 (3.34)

POAG, primary open angle glaucoma; OH, ocular hypertension; M, male; F, female; logMAR, logarithm of the minimum angle of resolution; D, dioptre; MD, mean deviation; NSAID, non-steroidal anti-inflammatory drug.

acuity was −0.04 (0.14), the mean spherical equivalent was −1.17 (3.86) D, and the mean MD value was −1.73 (5.00) dB. There were no statistically significant differences in the distribution of these parameters between the NSAID and control groups. All 13 patients completed the protocol, and there were no remarkable changes in visual acuity, anterior segment of the eye, or fundus compared with those before the additional administration of ophthalmic solution, and there were no adverse effects observed throughout the course of the study.

Effect of additional administration of NSAID ophthalmic solution

The mean IOP before latanoprost administration in the NSAID group was 22.6 (4.8) mm Hg, the mean IOP reduction by latanoprost administration was 24.2% (8.7%) (range 13%–35.5%). Although all patients demonstrated a satisfactory response, there were differences in the rates of IOP reduction among the patients examined.

The baseline IOPs were 17.0 (2.6) mm Hg in the NSAID group and 16.92 (2.94) mm Hg in the control group. The difference in the mean IOP was 0.08 (1.24) mm Hg, and no significant differences were observed (the Mann-Whitney U test: $p = 0.9$).

The IOP after 6 weeks' additional administration of NSAID ophthalmic solution in the NSAID group was 18.08 (3.04) mm Hg, indicating a significant increase compared with the IOP of 17.0 (2.6) mm Hg before the start of co-administration ($p = 0.028$). On the other hand, in the control group, there were no significant changes in IOP even after the additional administration of NSAID ophthalmic solution, and IOP demonstrated a decreasing trend.

Although there were no significant differences in IOP between the two groups after the start of administration of NSAID ophthalmic solution, the IOP in the NSAID group was higher than that of the control group at all measurement times after the start of additional administration, and that trend was continuously observed even after administration was discontinued (fig 2).

An assessment of the differences in IOP between the two groups revealed that the IOP in the NSAID group was higher than that in the control group at all measurement times following the start of additional administration, and that difference reached a maximum of 1.08 (1.75) mm Hg after 4 weeks of additional administration ($p = 0.032$). That difference was also observed following discontinuation of administration (fig 3).

Factors involved in effect of NSAID on IOP reduction by latanoprost

A significant positive correlation ($r = 0.59$, $p = 0.03$) between baseline IOP and IOP difference between NSAID group and control group during the period of additional administration was observed (fig 4). There were no significant correlations observed among age, sex, MD values, refractive error, or amount of change in IOP.

DISCUSSION

This study clearly demonstrated that ophthalmic NSAID inhibits the IOP reduction by latanoprost ophthalmic solution in glaucomatous eyes. These results agreed with those of our previously study,[10] which used healthy volunteers and Taniguchi *et al*,[11] who used rabbits, but differed from that of Sponsel *et al*,[12] where no inhibition of the IOP reduction by latanoprost ophthalmic solution was observed in glaucoma patients given latanoprost ophthalmic solution in one eye and brimonidine ophthalmic solution in the other eye, followed by oral administration of indomethacin for 2 weeks. The possible reasons for the difference in results include differences in the type of NSAID used, differences in the administration method, and differences in the duration of the co-administered period. According to our results, the inhibitory effect of bromfenac sodium hydrate was not significantly observed at week 2, but peaked at weeks 4–6 and persisted until week 12, which is the time of completion of administration of ophthalmic NSAID. Thus, the difference in the duration of the observation period may have contributed to the difference in our results from those of Sponsel *et al* who conducted measurements after the 2 week oral administration of indomethacin; however, the precise reason is unknown.

The reasons for using bromfenac sodium hydrate as the ophthalmic NSAID in this study are as follows: it demonstrates an inhibitory action on PG biosynthesis in rabbit iris ciliary bodies that is 3.8 times more potent than indomethacin and 10.9 times more potent than pranoprofen[13]; it has been shown to have no effect on the IOP[14]; and it is considered to be preferable for investigating the inhibitory effect of endogenous PGs. However, it will be necessary to study the effects of other NSAIDs in the future.

Sodium hyaluronic acid was used as the control drug in this study because the production of endogenous PGs has

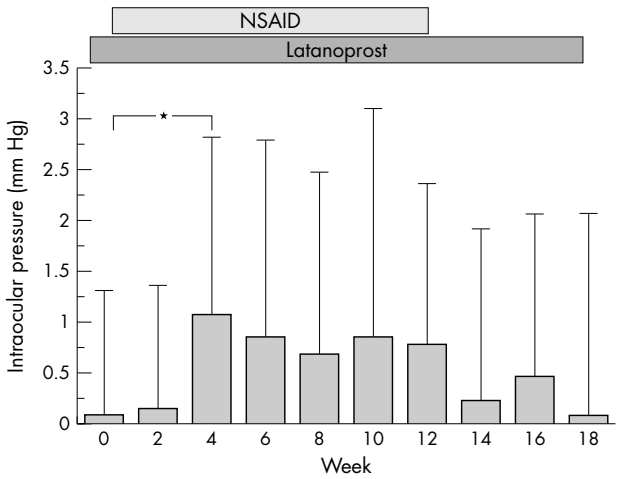

Figure 3 IOP difference between NSAID group and control group. NSAID, non-steroidal anti-inflammatory drug, *p = 0.032.

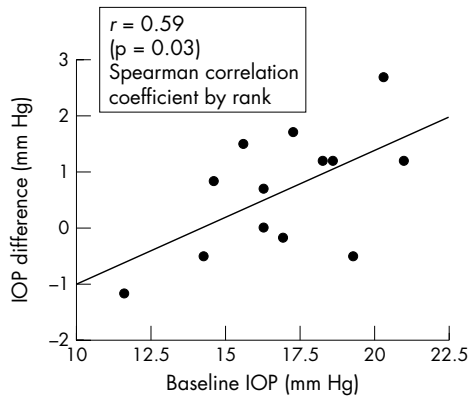

Figure 4 Correlation between baseline IOP and IOP difference during co-administration between NSAID group and control group. NSAID, non-steroidal anti-inflammatory drug, IOP, intraocular pressure.

been reported to be associated with benzalkonium chloride.[15 16] Bromfenac sodium hydrate contains 0.005% benzalkonium chloride, whereas sodium hyaluronic acid contains 0.003% benzalkonium chloride. Thus, the benzalkonium chloride concentrations of the two drugs are considered to be nearly equal.

In addition to reports describing the use of $PGF_{2\alpha}$ related drugs,[1–3 8–10] the relation between glaucoma ophthalmic solutions and endogenous PGs has also been described in other reports, including that by Kaplan-Messas *et al*,[17] who reported that endogenous PGE_2 is produced in isolated human iris upon administration of ophthalmic solution containing 2% pilocarpine and 1% adrenaline (epinephrine). In addition to the report by Yousufzai *et al*,[7] which described the release of endogenous PGE_2, PGD_2, $PGF_{2\alpha}$, and arachidonic acid (AA), there are some reports describing the release of PGE_2. There are also some reports suggesting that endogenous PGs have a role in assisting the IOP reduction by exogenous PG administration.[1–3 8–11]

With respect to PGE_2, although the PGE_2 analogue, RS18492, has been reported to initially increase IOP and subsequently decrease it by approximately 10% in human eyes,[18] it has also been reported to lower IOP by administration after latanoprost in monkey eyes.[19]

In addition, although endogenous PGE_2 is produced following latanoprost administration in cultured bovine iris melanocytes, since such endogenous agents as substance P and neuropeptide Y, which increase vascular permeability,[9] were not produced, these were unlikely to have had an effect on the IOP in this study.

Regarding the production of various endogenous PGs in the human eye, although the precise mechanism of their production, including to what extent they are actually released in the eye, and what types of PGs act in what manner to have an effect on IOP, is unclear, as indicated by the results of this study, the fact that the IOP reduction by latanoprost was inhibited by bromfenac sodium hydrate ophthalmic solution, which has a potent PG inhibitory effect, makes it possible to surmise that the auxiliary part played by various endogenous PGs produced by latanoprost administration in the IOP reduction was suppressed.

The fact that a positive correlation was observed between the baseline IOP and the differences in left and right IOP during administration of ophthalmic NSAID indicates that the effect of endogenous PGs on IOP reduction by latanoprost may increase with the intensity of the IOP reduction by latanoprost.

Although the inhibition of the IOP reduction by latanoprost by bromfenac sodium hydrate may be considered to have insufficient clinical significance because the difference in IOP between the control group and the NSAID group was only an average of 1.08 mm Hg, it may be an important finding in terms of considering the mechanism by which latanoprost reduces IOP. In addition, it is necessary to study the effects of NSAIDs on other PG related ophthalmic solutions used for the treatment of glaucoma.

Since ophthalmic NSAIDs are frequently used in routine clinical settings, their action should be taken into consideration when administering ophthalmic NSAIDs to glaucoma patients for long periods of time.

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Proprietary interest: none.

Ethics approval: This study was conducted in accordance with the Helsinki declaration after receipt of approval from the ethics committee of Yamanashi University. The subjects were adequately informed of the study and written consent was obtained from all of them.

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